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Engineered Nanoparticle Aerosol Foam Formulation for Skin Diseases

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Abstract : ***The objective of the work is to formulate, optimize and evaluate "Itraconazole nanosuspension as aerosol foam formulation" for the treatment of skin diseases such as Cellulitis, Erysipelas, Impeigo and Blastomycosis, Histoplasmosis, Onchomycosis, etc. The solubility of poorly soluble itraconazole can be improved through nanosuspension process and also the absorption rate and bioavailability of drug can be enhanced by means of aerosol foam dispersion at the site of application.***

Keywords : ***Itraconazole, nanosuspension, wet milling, foam.***

Introduction

Growing interest in dermatology make it achievable for different researches regarding skin diseases and come out with various solutions where the most valuable outcome of those studies is "Foam technology" which is widely believed to be the future for dermatological drugs as if considered by the pharmaceutical giant Foamix. Everyone is familiar with the role of skin as it acts as a protective barrier as well as has so many functions and in particularly provides an alternative route for drug delivery.[1] More frequently it gets affected by the external agents or microorganisms which can be treated with various active agents like anti-fungal, anti-bacterial, keratolytic agents, anti-microbial, steroidal anti-inflammatory drugs, antivirals, vitamins, anti-histamines, etc. [2] Topical formulations are preferred in these cases to treat the patients as it is more convenient over other formulations including tablets, capsules and injections. Plenty of traditional topical formulations like creams, ointments, gels and patches are available in the market to treat skin diseases either via dermal or transdermal delivery of drugs. Nowadays it includes some other novel categories too for treating the infections those includes sprays, foams, multiple emulsions, macroemulsions, liposomal formulations, transferosomes, niosomes, ethosomes, glycospheres, etc., and our attempt is to use the novel method Foam technology where foam acts as vehicle to deliver drugs at the site of infection in a superior way.[3] It results in enhanced absorption because of its presence over skin for a longer time, improved patient compliance and will not leave any residue over the skin.

Drug of choice is Itraconazole, a triazole antifungal agent which has the better effect over most of the fungal species such as dermatophytes, yeasts, Aspergillus spp. Penicillium spp, dimorphic fungi and different phaeohyphomycetes. It is available as capsules, suspensions and I.V injections having bioavailability of 55% when taken along with full meal. It is insoluble in water which is considered to be the reason for its unavailability in different formulations and lipophilic nature of the drug also one of the causes for its inaccessibility. [4,5] To overcome this problem its solubility should be improved which can be done by nanosuspension process, Nanosuspension are the colloidal dispersions of nano-sized drug particles which aid in improved solubility and dissolution rate of the poorly soluble drugs. [6] Preparation of nanosuspensions carried out either by bottom up technology or top down technology where in first case nano-sized particles are settled down from the solution by precipitation process and in second case larger particles are converted to nanoparticles by different methods comprises wet milling, [7,8] high pressure homogenization. As the particle size decreases the adhesive properties of the particles will be enhanced that result in better dissolution with improved drug delivery. [9]

The objective of the current research is to formulate a 'Nanosuspension aerosol foam formulation containing antifungal agent Itraconazole' for the treatment of skin diseases such as Cellulitis, Erysipelas, Impeigo and blastomycosis, histoplasmosis, onychomycosis, etc., And attempt is to increase the absorption rate and bioavailability by increasing the solubility of the poorly soluble drug through Nanosuspension process and aerosol foam.

Materials and Methods

Itraconazole was obtained as a gift sample from Glukem Pharmaceuticals, Hyderabad. Pluronic F68 and Pluronic F127 were obtained from Sigma Aldrich, Polyvinyl alcohol from Otto and

Sodium alginate of chemspure was used.

Preparation of Nanosuspension

Wet milling technique was used for the preparation of nanosuspension where ball mill of inhouse designed was used. The milling media contains surfactants, stabilizing agent, drug and distilled water. [10,11] Two types of milling media was used where the one containing combination of Polyvinyl Alcohol and Pluronic F68 as surfactants; the other holds only Pluronic F127. Along with these surfactants, the milling media also contains 1% w/v of sodium alginate and 100 mg of drug which were added together in the distilled water of 150mL. Above mixture was grinded in ball mill using 29 iron balls of 3mm diameter at 800 rpm which was measured using Digital Tachometer (Lutron DT-2234C) for 6 hours and the final mixture was collected which was then centrifuged at 9000 rpm for 30 min to settled down the micro particles.

Preparation of Aerosol foam

The obtained nanosuspension was then compressed with propellant by compress filling method in the canister in order to get the product outcome in the form of foam and the propellant used was hydro fluorocarbon: 1, 1, 1, 2 –

tetrafluoroethane along with 0.1% w/v of sodium lauryl sulphate as a foaming adjuvant. [12]

EVALUATION OF NANOSUSPENSION

Preformulation studies

- **Melting point**
  Melting point of the pure drug was determined by capillary tube method where the pinch amount of the sample was filled in the one end sealed capillary tube and was kept in the melting point apparatus (Ajay^{TM}) along with thermometer in order to measure the melting point. The initial point at which the sample starts melting and final point where it completely melted is noted and tabulated.
- **Solubility**
  10mg of drug was weighed and dissolved in 0.5mL of solvents and 1mL of different buffers. The solvents include acetone, gluteraldehyde, methanol, ethanol, isopropyl alcohol, dimethyl sulphoxide and acetic acid whereas the buffers used were NaOH (1N, 0.1N), 0.1N HCl, phosphate buffer (of pH 4.75, 6.8, 7.2), polyethylene glycol (400, 600) and water respectively. All these were kept in well closed air tight containers, once the initial amount got dissolved successive amount of samples were added until the media became saturated. Then the containers were placed in rotary shaker (Remi laboratory instruments, India) for 24 hours and to determine the solubility of drug samples[13] were filtered from which filtrate of appropriate amount was diluted to analyze in UV-Vis spectrophotometer in order to find out the quantity to be dissolved.
- **Partition Coefficient**
  Accurately weighed amount of 10mg of drug was dissolved in one phase and was shaken well in separating funnel with other partitioning solvents. Butanol, octanol, chloroform, dichloromethane, cyclohexane, benzene were all used as the organic phase and the aqueous phase comprised of water and phosphate buffer of three different pH 4.5, 6.8, 7.2 respectively. Total 10mL of each organic phase and aqueous phase was shaked for 30 minutes and kept aside for 5 minutes then the extract of upper and lower portions was collected separately. Partition coefficient[13] is further calculated using the following equation:

$$\text{Log P} = \frac{\text{Concentration of Organic phase}}{\text{Concentration of Aqueous phase}}$$

pH

pH of the nanosuspension was measured using pH meter (Susima pHmeter MP-1 PLUS) by placing the glass electrode directly in the beaker containing formulation and the values were noted down from the digital meter.

Viscosity

Viscosity describes the resistance to fluid's flow which helps in determining the behavioral property of fluids. The viscosity of the nanosuspension was determined using Brookfield viscometer DV-II + pro extra (Brookfield LV, USA) using spindle no.62 in different rpm (20, 30, 50, 60, 100, 150, 200) in triplicate at room temperature. [14]

Particle size and charge

Particle size and zeta potential of the prepared nanosuspensions[15] were analyzed to know about the solubility, dissolution rate and physical stability where the characterization was done using Malvern zeta analyzer. It was proved that changes in size of the particles changes the dissolution velocity as well as saturation solubility while the polydispersibility index correlates the physical stability of nanosuspensions. Zeta potential was considered as the indirect measurement of diffusion layer thickness which also helps in understanding about the physical stability of the formulation influenced by stabilizers and also the drug used.

Drug content

Drug content[16] in the formulation was determined by pipetting out 1mL of sample which was then diluted to 10mL using 0.1N HCl, further analysis was done at UV- Vis spectrophotometer (Evolution 201, Thermo Scientific, USA) at 254nm.

***In-vitro* dissolution studies**

The dissolution behavior of nanosuspension was assessed by dialysis membrane method using USP/NF XXIV type-1 rotating basket method (DS8000, Lab India). [17] 2mL of sample was transferred in the tube which was sealed with dialysis membrane on one side and was kept in basket in such a way that the membrane should dip in the 100mL medium kept in the vessel where water, 0.1N HCl and phosphate buffer (pH 6.8) were used as the dissolution medium. Temperature was maintained at 37±2º C with stirring rate of 50 rpm and sample aliquots of 10mL was withdrawn for every one hour up to 6 hours with the simultaneous replacement of same amount of fresh media each time to maintain the sink condition and then the samples were analyzed spectrophotometrically at 254nm where all the measurements were performed twice. The concentration of drug present in the formulation was estimated using the standard calibration curve and the percentage drug released at each time points was calculated from the data.

Drug release kinetics

The mechanism of drug release from the formulation was studied by fitting the obtained dissolution data to various mathematical kinetic models such as zero-order, first order, Higuchi, Korsmeyer-Peppas and Hixon- crowell models, the criteria for selecting the most appropriate model are chosen on the basis of goodness of fit test. R^2 values obtained from the respective plots were noted and also the slope value obtained from the Korsmeyer-Peppas kinetics model, the mode of drug release from the dosage form was checked. [18]

Fourier Transform Infrared Spectroscopic Studies (FT-IR)

The Fourier transform infrared analysis was used to identify the possible interaction that occurs between chemical bonds of drug and polymer. [19] Here we did the analysis in Attenuated Total Reflectance (ATR) mode[20] which was the surface sensitive analytical technique detecting molecular species through absorption spectroscopy within an exponentially decaying evanescent field generated at the surface of an appropriate total internal reflection element. Molecule present over the surface of the reflection element

was determined at mid infrared wavelengths. The samples absorb energy which results in attenuation of the evanescent wave after that IR beam was spotted in the detector and the spectrum was recorded.

Evaluation of Foam

Relative foam density[21]

The pressurized container was shaken well and small amount of foam was dispensed as waste. Take flat bottomed dish with approximate volume of 60mL and was uniformly filled with foam, after the foam had completely expanded level off it by removing excess foam with slide and the dish was weighed (BL- 220H, Shimadzu). Similarly mass of the same volume of water was determined by filling the dish with water and the weight was noted.

Relative foam density is equal to the ratio:

$$\frac{m}{e}$$

Where, m= mass of the test sample of foam (g)
e= mass of the same volume of water (g)

Visual assessment of foam

Foam structure and foam characteristics can be depicted by visual aid it includes bubble size, shape, clarity, density and collapse time [22] respectively. The formulation in the canister was sprayed and was visualized for the bubble size in order to identify its coarser or fine appearance of the foam structure as well as the clarity of foam was observed as it plays a role in aesthetic value. Collapse time can be noted after the foam was sprayed over the dish/ hand and the time taken by the bubbles to disappear completely to leave the formulated drug over the skin.

Determination of drug content per puff

Drug content in the delivered foam was determined by dispensing one puff of foam from the container into the beaker. Then 0.1N HCl was added to the sample and make up to 10mL where further analysis was done under UV-Vis spectrophotometer at 254nm.

RESULTS AND DISCUSSIONS

Preformulation studies

- **Melting point**

The pure drug was filled in the one end sealed capillary tube and visually examined. The initial and final temperature was noted from the thermometer and tabulated. Melting point of the drug was found to be in the range of 161.6±0.57º C to 180±2 º C.

- **Solubility**

Solubility test was carried out after it reaches the saturation state and the samples were collected individually; Saturation solution was one which attains equilibrium between the solution and the excess substances. [23] 0.1mL of saturated solution was making up to 100mL and analyzed spectrophotometrically at 254 nm that was shown in table 1; There it was found that the solubility of the drug in 0.1N HCl, water, PEG 400 and PEG 600 was found to be better than other buffers but in case of 0.1N HCl solubility was observed as low because of its diluted form as it was found to be freely soluble in concentrated HCl. Considering solvents the pure drug shows notable solubility in acetone and gluteraldehyde than other solvents. Whereas nearly in all researches for the quantitative determination studies methanol was used as solvent system but in present study it was noticed that the drug was insoluble in methanol and ethanol.

- **Partition coefficient**

Partition coefficient was determined by shake flask method which was considered to be a better one to measure the lipophilicity of solutes. It was found from the table 2 that the drug having the log P value in between the range of 0.8-3 for different combinations of partitioning solvents. According to Lipinski, compounds with log P values between 1 and 3 shows good absorption likewise the obtained result proves the same. [24] From the log P values it was obvious that the drug was highly lipophilic in nature be the evidence for its ability to cross the biological membranes in an efficient way with good absorption. Among the results dichloromethane: water combination shows log P value of 3.09 in addition other combinations like dichloromethane: PBS (pH6.8) and octanol: water shows merely 2.79 and 2.72 respectively.

Different combinations of itraconazole nanosuspension was prepared as per the proportions listed in the table 3 where IC be the combination of Itraconazole with Polyvinyl alcohol (PVA) plus Pluronic F68 likewise IP represents formulation containing only Itraconazole and Pluronic F127.

pH

For better absorption of formulation via topical route it should meet pH ranging between 4- 6.5 which was also related to the pH of the surface of stratum corneum, [25,26] and from the table 5 it was found that the itraconazole nanosuspension too have the similar pH values in the range between 5.9- 6.87 which evident the possibility of easy permeability of drug across stratum corneum.

Viscosity

Viscosity helps in determining the flow behavior of fluids, rate of flow was directly related to the applied stress that is viscosity change with change in shear stress then it was referred as Newtonian fluids. [27] But from table 4 it was observed there was an increase in viscosity with increase in shear stress it might be because of disperse systems in the nanosuspension as this was referred as dilatant flow and exhibits shear thickening effect however if the measuring gap was longer laminar but becomes turbulent this might be falsely suggest dilatancy. It was also well seen that there was an increase in viscosity with increase in concentration of the surfactants. Here the formulation IP3 had a viscosity range between 4.5- 14.2 cP; viscosity range of IC3 was found to 10-14.5 cP as it was of more viscous, flow rate would be slow that make the formulation to retain over skin for a longer period.

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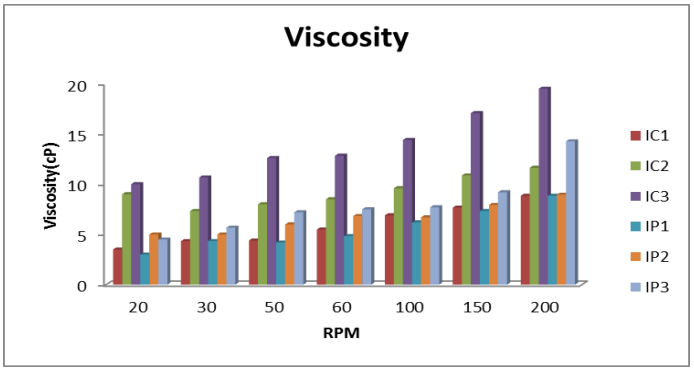

Figure1: viscosity of prepared formulations.

Particle size and charge

The particle size distribution and the stability values were tabulated in table 5, that the formulations IC1, IC2 and IC3 had the particle size distribution falling in the range of 427-896nm whereas for formulation containing only pluronic F127 having the distribution range 560-637nm. Among these IP1, IP2 and IC2 formulation falls under the nanoparticle range of 200-600nm where incase of IP1 as well as IP2 the effective size reduction was due to the surfactant Pluronic F127; however particle size distribution of IC1, IC2 and IC3 was relatively less when compared with the other formulations due to the combination of ionic and non-ionic surfactants. Considering stability IP2 and IP3 gives better results with zeta potential of -21.8mV and -22.8mV which proves that they were having good stability because maintaining ZP at ±20mV was considered as sufficient value for stable formulation with combined electrostatic and steric stabilization. [28] The increased zeta potential was due to the physical adsorption of Pluronic F127 molecules to the drug surface, it was also confirmed that increasing concentration would improve stability but decrease in stability of IC1 and IC2 was because of influence of the surfactant combinations. In case of polydispersibility index values between 0.1-0.25 indicates a narrow size distribution and greater than 0.5 was referred for wider distribution, while comparing these values with itraconazole nanosuspension IC3, IP1 holds the level at narrow range and with other formulations it was contrary.

Drug content

For determining drug content diluted samples were analyzed at UV spectrophotometer at 254nm and the absorbance values were noted. From these values respective concentrations are calculated using the calibration curve, furthermore multiplying dilution factor with calculated concentration value gives out the amount of drug present in the appropriate volume of the solution.

***In-vitro* dissolution studies**

Six hour dissolution study for the nanosuspension was carried out with rotating basket method in three different dissolution media like Water, Phosphate buffer 6.8 and 0.1N HCl. As this drug shows better solubility in 0.1N HCl it was used as one of the medium for dissolution study and from the figure 1 it was observed that IP1 had a higher drug release followed by IP2 which shows a gradually increased release whereas very low drug release was noticed from the IC1. Phosphate buffer with pH 6.8 was used as one of the medium as this formulation was intended to apply topically; IP3, IC3 shows a gradual increase in drug release and here too release from IC1 was low because of influence of viscosity and wider particle size distribution. Considering water as dissolution medium in general all formulations showed a reasonable drug release and the influence of size distribution of particles over drug release was also observed. Both formulation IP1 and IP3 had a better drug release compared with IC1and IP2. Dissolution had its own role in formulating dosage forms because better dissolution leads to enhanced drug absorption. [29]

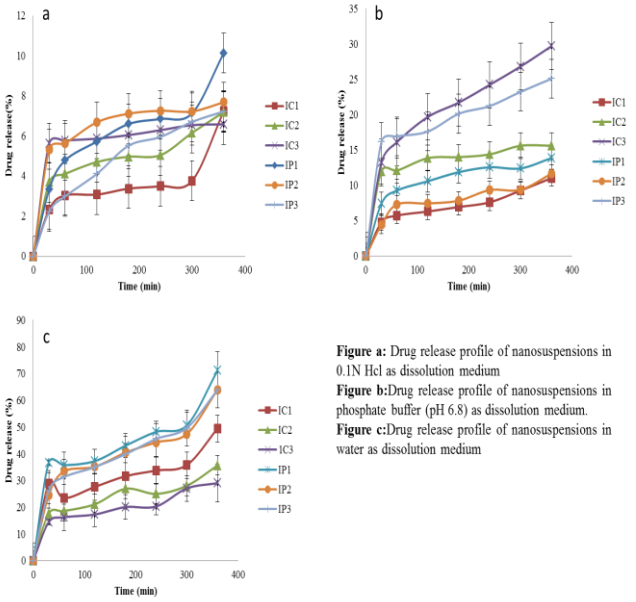

Figure a: Drug release profile of nanosuspensions in 0.1N Hcl as dissolution medium
Figure b: Drug release profile of nanosuspensions in phosphate buffer (pH 6.8) as dissolution medium.
Figure c: Drug release profile of nanosuspensions in water as dissolution medium

Mechanism of drug release

The models generally chosen to explain about the mechanism of drug release were Zero order, First order, Higuchi, Korsmeyer-peppas and Hixon crowell. The n value of Korsmeyer- peppas was used to characterize diffusional mechanisms of drug release where the values be in the respective range like, if n≤0.45, fickian diffusional release would occur while for 0.45> n< 0.85 the release was non-fickian. [30] For 0.1N HCl as dissolution medium IP1 formulation had better drug release and having R^2 value of the respective kinetic models were 0.605, 0.625, 0.927, 0.944, 0.619 with n- value of 0.394 (table 6) which was equivalent to n≤0.45 condition confirms that the formulation follows fickian diffusional mechanism. In case of water, IC3 plus IP3 formulations had the higher release with R^2 value that was observed from the table 7 as 0.420, 0.507, 0.879, 0.947, 0.479 and 0.576, 0.729, 0.926, 0.953, 0.686; where n values of both nanosuspensions proved it as a fickian diffusion. Considering phosphate buffer with pH6.8 in table 8, IP1 as well as IP3 shows a better release with fickian mechanism having R^2 values 0.078, 0.151, 0.807, 0.995, 0.127 and 0.046, 0.085, 0.728, 0.982, 0.043 respectively. Considering R^2 as a goodness of fit parameter in order to determine the mechanism followed by the nanosuspension system it was found that all six formulations follow Korsmeyer- peppas model in all three media.

Fourier Transform Infrared Spectroscopic Studies

The FTIR spectrum [31] of pure itraconazole and prepared nanosuspension was shown in the figure 4, where the spectrum of pure drug shows the characteristic peaks at 2823.21-3127.16cm^{-1} due to –C-H- vibrations. Peak at 3069.07cm^{-1} shows the stretching of aromatic rings, range between 3127.16- 3384.62 cm^{-1} was because of N-H stretching of amide groups. Peaks occurs at 711.96- 899.01

cm^{-1} arises due to the groups occupying different positions on benzene ring; among these inspecific band between 824- 852 cm^{-1} shows the para substitution. –C-O stretching was characterized at 1228.32- 1052.97 cm^{-1}, -C-N- stretch of alkyl group was observed at 1043-1185 cm^{-1}, peak at 1772.18 cm^{-1} was due to stretching of –C=O- and spectrum from 561-762cm^{-1} indicating C-Cl stretching respectivelsy. While considering the major peaks of the formulation all spectrums were closely related to the pure drug here N-H stretching of amides was observed at 3429.21 cm^{-1}, peak at 1638.80 cm^{-1} due to stretching of –C=O, similarly peaks at 1262.05 cm^{-1} indicating –C-O stretching, -C-N stretching of alkyl amine was noticed at 1101.12 cm^{-1} and the band at 671.54 cm^{-1} shows the C-Cl stretching. Comparing both pure drug and itraconazole nanosuspension spectrum it was found that there was a negligible peak shift due to delocalization of Pi electrons. Broader peak appearance in itraconazole nanosuspension spectrum was due to slight variations in vibrational frequency as well as due to superimposability of polymers with
drug.

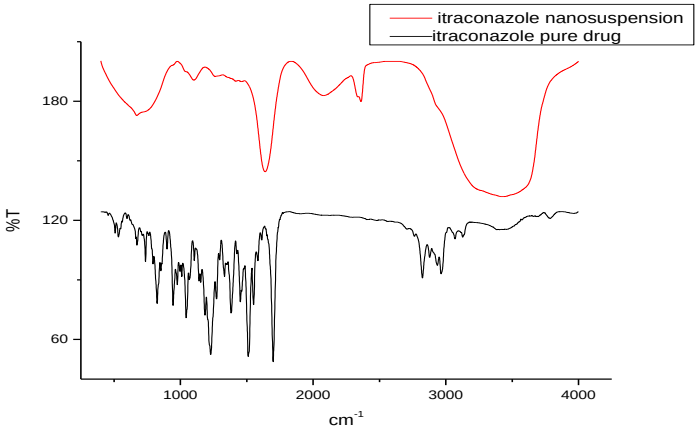

Figure 2: FTIR spectrum for itraconazole pure drug and nanosuspension

Evaluation of foam

Pharmaceutical topical foams were prepared by filling propellant hydrofluorocarbon inside the pressurized container in such a way to deliver foam when the actuator was pressed. Among the six formulations, three formulations (IP1, IP3 and IC3) were selected on the basis of its physical stability and particle size distribution. Surfactants play a vital role along with propellants because the stability of foam was totally depends on surfactants and propellants helps in dispersion of drug within air/ liquid interface which consecutively increase the release of drug from the nanosystem.

Relative foam density Relative foam density was determined using a dish of 57mm in diameter and 7mm thickness, where the dish was used to measure the mass of the foam sample and water. Dish weight was tared after that the foam was dispensed over the dish and the weight was noted down similarly the weight of same volume of water was also noted. From the values obtained relative foam density was calculated by dividing mass of foam sample and mass of water which had the values in the range between 0.08-0.13 shown in the table 9. **Visual assessment**

The obtained foams were visually evaluated to determine different parameters including bubble size, shape, clarity and collapse time.

Bubble size

Foams were produced from the pressurized containers by the actuation of valve, where the bubble formation was due to surfactant concentration. Surfactants in the container might exist as single phase system or multi phase system which reduces surface tension between the bubble interface results in its stability. Bubble size of the dispensed foam was found to be small in size as the time goes off it becomes smaller because of pressure inside the bubble and finally gets ruptured due to thinning effect in bubble walls. [32]

(ii) Shape and clarity

Dispensed foam was evaluated for its shape and clarity which was found that the foam of IP3 formulation was appear to be in white; while for IC3 and IP1 formulation foam was viewed as yellowish brown colour, in the case of clarity all the three formulations was opaque in nature. According to *Albert et al* whom described the quality scale for foam as per their results the acquired foam came under the rating 1 i.e., foam was fine, with overtime it became coarser bubble. Similarly Tamarkin.D *et al* also graded foams into six categories among those the nanosuspension foam formulation was observed under Good grade because it appears as rich and creamy with small bubble size which didn't became watery at the same time it maintains to be creamy while applying over the skin.

(ii) Collapse time

In order to determine the collapse time of foam it was sprayed over the dish relatively its time was noted. Bubbles formed were of quick breaking which was because of partitioning of surfactant in aqueous phase resulted due to localization of surfactant in the propellant phase. Bubble collapses due to drainage in foam which reduces the thickness of bubble walls there occurs the coalescence of bubbles results in rupture. [33] For the present formulation time ranges from 15-20 minutes.

(iii) Drug content per puff

Drug content of foam per puff was determined by ejecting 2mL of foam which was make upto 10mL with 0.1N HCl. Samples were further analyzed spectrophotometrically at 254nm and were determined as 0.98% for IC3; whereas for IP1, IP3 holds the value of 1.05% and 2.12% respectively.

Figure 4: Images of containers containing nanosuspension compressed with propellant.

Figure 5: Picture of foam with rich and creamy appearance of formulations IP1, IP3 and IC3.

Table 1: composition of different ingredients used for the preparation of nanosuspension

Ingredients/formulations	IC1	IC2	IC3	IP1	IP2	IP3
Drug (mg)	100	100	100	100	100	100
Polyvinyl alcohol(%)	0.5	1.5	2.5	-	-	-
Pluronic F68 (%)	0.5	1.5	2.5	-	-	-
Pluronic F127 (%)	-	-	-	1	3	5
Sodium alginate (%)	1	1	1	1	1	1
Sodiumlauryl sulphate(%)	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water (mL)	150	150	150	150	150	150

Table 2: Comparison of Particle size, Polydispersibility index, Zeta potential, drug content and pH for six formulations.

Formulation	Average particle size (d.nm)	Poly-dispersibility index	Zeta potential (mV)	Drug content (%)	pH
IC1	896.4	0.613	-16.7	95.96	6.253±0.01
IC2	427.9	0.422	-13.2	91.42	6.29±0.03
IC3	657.2	0.447	-15.9	97.29	5.99±0.01
IP1	590.9	0.275	-12.6	63.04	6.68±0.02
IP2	560.1	0.710	-21.8	79.59	6.87±0.2
IP3	637.9	0.929	-22.8	75.47	6.81±0.05

Formulation/ Parameter	Relative foam density	Collapse time (min)	Drug content per puff (mg)
IC3	0.089	20	0.98
IP1	0.1	15	1.05
IP3	0.131	20	2.12

Table 3: Foam evaluation for various parameter

Conclusion:

Topical formulations play a vital role in treating skin diseases because of its direct application at the targeted site even to treat systemic infections also we can treat through skin itself by using transdermal formulations. Among all other formulations the growing interest was towards foam formulations because of supreme advantage over other formulations however product availability in market was less due to nature of new chemical entities which need various optimizing procedure in order to get stable product with expected outcome. In the present work itraconazole nanosuspension foam was formulated to treat the fungal infections by applying directly over the infected area. As the drug belongs to class II of BCS classification its solubility was improved through nanosuspension process which in turn results in better dissolution of drug whereas foam improves its absorption over skin by increasing its retention time by avoiding common problems like hepatic metabolism and gastrointestinal destruction. Specifically in case of itraconazole the application of drug through foam will be effective, as the drug itself found to be accumulated in hair follicles after its administration so applying it topically gives out improved results with enhanced therapeutic action. By doing further studies regarding foam in depth about their role as vehicle, influence of surfactants over the stability, propellants significance will help in optimizing a better formulation to get best results.

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